RESPONSE

I. Amendment to the Specification

The fifth Action at page 2 requests correction of the specification to indicate that TAXOL™ is a trademark. Appropriate corrections have been made to the specification.

II. Status of the Claims

Prior to the fifth Action, claims 4-9, 23-27, 41 and 49-88 were pending and have been examined. Claims 5, 24, 26, 56, 69, 74 and 86 are said to be allowable, but objected to as dependent on a rejected base claim (fifth Action at summary page; page 11). However, as claim 69 and claim 74 are independent claims not subject to rejection, claim 69 and claim 74 are also properly allowed.

Presently, claims 4, 24, 68, 70, 71, 73, 75-77 and 80-82 have been amended without prejudice or disclaimer. No claims have been cancelled. Claim 89 has been added, which is fully supported by the application as filed and unified with the examined claims. Should any small entity fees be necessary for the new claim, such fees should be deducted from Peregrine Pharmaceuticals, Inc. Deposit Account No. 50-3493/4001.002299.

Claims 4-9, 23-27, 41 and 49-89 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

III. Support for the Claims

Support for the revised and new claims is to be found throughout the specification and claims of the original and parent applications.

Claim 4 has been amended to clarify that the first antibody, or antigen-binding fragment thereof, kills at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promotes coagulation in at least a portion of the blood vessels of the vascularized tumor,

destroys or occludes at least a portion of the blood vessels of the vascularized tumor, induces necrosis in at least a portion of the tumor, induces tumor regression or induces tumor remission. This is supported throughout the specification as filed, *e.g.*, at least at pages 7-16, particularly page 12, lines 1-12.

Allowable claim 24 has been revised to place this claim into independent form.

Claim 68 has been amended to more particularly recite the therapeutic effects, and is supported as set forth above for claim 4.

Claim 70 has been revised to be an independent version of allowable claim 5, which provides exemplary support.

Claim 71 has been amended to recite the therapeutic effect of killing at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, and is supported as set forth above for claim 4.

Claim 73 has been amended to more particularly recite the therapeutic effects, and is supported as set forth above for claim 4.

Claim 75 has been amended to recite the therapeutic effect of promoting coagulation in at least a portion of the blood vessels of the vascularized tumor, and is supported as set forth above for claim 4.

Claim 76 has been amended to recite the therapeutic effect of inducing tumor regression, and is supported as set forth above for claim 4.

Claim 77 has been amended to recite the therapeutic effect of inducing tumor remission, and is supported as set forth above for claim 4.

Claim 80 has been amended to more particularly recite the therapeutic effects, and is supported as set forth above for claim 4.

Claim 81 has been revised to be an independent version of allowable claim 56, which provides exemplary support.

Claim 82 has been amended to more particularly recite the therapeutic effects, and is supported as set forth above for claim 4.

Finally, independent claim 89 reflects claim 4 prior to the present amendment, which provides exemplary support.

It will therefore be understood that no new matter is included within any of the amended or new claims.

IV. Applicants' Interview Summaries

A telephone interview for the present application was held on March 15, 2007. As noted in the Examiner's and Applicants' Interview Summaries already of record, the March 15, 2007 telephone interview concerned the non-entry of the after-final amendment, for which agreement was not reached.

However, in the March 15, 2007 telephone interview, Examiner Fetterolf and SPE Foley confirmed the earlier agreement that all claims except claim 73 (and claims dependent thereon) were allowed. See, Applicants' interview summaries of December 12, 2006 and Applicants' response to the fourth and final Official Action submitted January 08, 2007.

Following the March 15, 2007 telephone interview, further telephone interviews were held between Examiner Fetterolf and Applicants' representative, Shelley Fussey. During these telephone interviews, Examiner Fetterolf confirmed the allowance of all claims except claim 73 (and claims dependent thereon). Examiner Fetterolf further indicated that claim 73, drawn to monotherapy (and claims dependent thereon), was likely to be entered and found allowable

should Applicants file a Request for Continued Examination (RCE), although such an outcome could not be guaranteed.

V. Prosecution History and Rejections Overcome

In the first Action, each of claims 5, 8-10, 23-26, 41, 57, 58, 61, 62, 64 and 65 were found to be allowable. Many of those allowable claims were placed into independent form in Applicants' first response. The first Action cited Fishman *et al.*, *Int. J. Oncol.*, 10:901-904, 1997 ("Fishman") in a rejection under 35 U.S.C. § 103(a) in combination with Tschmelitsch, which rejection was overcome by Applicants' first response.

The second Action entered non-final rejections against most of the formerly allowable claims, but indicated claims 23-26 and 72-74 to be allowed or allowable. The second Action rejected several claims under 35 U.S.C. § 103(a) over U.S. Patent No. 6,300,308 to Schroit in combination with U.S. Patent No. 5,725,856 to Hudziak, which rejection was overcome by Applicants' second response.

The third Action returned to Fishman, entering a § 103(a) rejection over Fishman in view of Holash *et al.*, *Oncogene*, 18:5356-5362, 1999 ("Holash") in combination with Hudziak or Hillman. The citation of Holash, a post-filing date reference, was essential to this § 103(a) rejection. The rejection was overcome by Applicants' third response.

The fourth Action did not include any rejections under 35 U.S.C. § 103(a). A telephone interview after the fourth Action resulted in agreement on allowance for all claims. In order to avoid duplicative claims, Applicants' fourth response revised independent claim 73 to be directed to monotherapy, rather than combination therapy. The earlier agreement on allowance for all claims did not extend to claim 73, as the issue of duplicative claiming had not been foreseen.

The amendment in response to the fourth Action was denied entry due to the inclusion of claim 73. The amendment was then entered upon filing an RCE.

Following entry of the RCE, a fifth Action has now been mailed, entering another series of § 103(a) rejections each relying on Fishman. Although these rejections no longer include the post-filing date reference, Holash, the reasoning is essentially the same as that relying on Holash and advanced in the third Action. Despite the new rejections, the present response shows that all pending claims are in condition for allowance.

VI. Claims Already Allowable and Allowed

The fifth Action indicates that each of claims 5, 24, 26, 56, 69, 74 and 86 are allowable, but objected to as dependent on a rejected base claim (fifth Action at summary page; page 11). In fact, as claim 69 and claim 74 are independent claims not subject to rejection, claim 69 and claim 74 are now allowed.

Allowable claim 26 was already represented by independent claim 74, which is allowed.

Allowable claim 86 was already represented by independent claim 69, which is allowed.

Allowable claim 24 has been converted into independent form and is thus now allowed.

The subject matter of allowable claim 5 is now recited in independent claim 70, which claim is thus now allowed.

The subject matter of allowable claim 56 is now recited in independent claim 81, which claim is thus now also allowed.

Accordingly, each of claims 70, 24, 81, 69 and 74 are already agreed to be allowed.

Claims 5, 26, 56 and 86 are still allowable.

VII. Summary of Other Patentable Features

The fifth Action withdraws all previous objections and rejections, including the written description and new matter rejections under 35 U.S.C. § 112, first paragraph. Applicants appreciate the withdrawal of these rejections.

Although many claims are newly rejected in the fifth Action, Applicants appreciate the examiner's guidance on overcoming the present rejections, particularly as set forth at page 10 of this Action. In addition, it is noted that Applicants' reasoning set forth below has previously been accepted as overcoming essentially the same rejections based on Fishman (see Applicants' third response, prompting withdrawal of all art rejections in the fourth Action).

In light of this guidance, Applicants elect to place the claims in condition for allowance using language indicated to be acceptable in the fifth Action at page 10, namely recitations of therapeutically effective that clearly distinguish over Fishman. All but one of the independent claims has been revised accordingly. Claim 89 is also in condition for allowance as the meaning of therapeutically effective set forth in the specification still distinguishes over Fishman.

All claims are therefore in condition for allowance, based upon the claims not subject to rejection and the present response, including the examiner's guidance on allowable claim language and all Applicants' reasoning.

VIII. Rejection Under 35 U.S.C. § 102(b)

Claims 73, 59 and 60 are newly rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fishman. Although Applicants respectfully traverse, the Action's concerns are overcome.

A rejection on the grounds of anticipation requires the disclosure, in a single reference, of every element of a claimed invention and requires that each and every facet of the claimed

invention be identified in the applied reference. *Ex parte Levy*, 17 USPQ2d 1461 (B.P.A.I. 1990); *Minnesota Mining & Mfg. v. Johnson & Johnson Orthopaedics, Inc.*, 24 USPQ2d 1321 (Fed. Cir. 1992).

Independent claim 73 first recites "*treating* an animal with a *vascularized* tumor by administering an antibody, or antigen-binding fragment thereof, which *targets* and binds to an aminophospholipid of an *aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor*". The therapeutically effective amount of the antibody is "an amount effective to kill at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promote coagulation in at least a portion of the blood vessels of the vascularized tumor, destroy or occlude at least a portion of the blood vessels of the vascularized tumor, induce necrosis in at least a portion of the tumor, induce tumor regression or induce tumor remission".

Dependent claim 59 recites that the antibody binds to phosphatidylserine of a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor, and dependent claim 60 specifies that the bound complex is a phosphatidylserine and β_2-glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor.

Fishman fails to disclose many important elements of the claims, and thus fails to anticipate the claimed invention.

In contrast to the fifth Action at page 2, Fishman does not teach *treating* melanoma, but only "an inhibitory effect on metastasis" (Fishman at page 903, column 1; third Action at page 13). Inhibition of metastasis is not equivalent to, and does not teach or suggest, methods for treating tumors, as in the presently claimed invention. See, *e.g.*, the Harris declaration already of record, which establishes that inhibiting metastasis is completely different from treating tumors

by targeting and destroying vessels, resulting in tumor necrosis and destruction, as in the present invention (Harris declaration throughout, *e.g.*, paragraphs 16 and 17).

Fishman also fails to teach treating any *vascularized* tumor. The fifth Action at pages 2-3 alleges that while Fishman does not characterize the melanoma as being vascularized, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art, citing both the present specification and *Bristol-Myers Squibb Company vs. Ben Venue Laboratories*, 58 USPQ2d 1508 (Fed. Cir., 2001). The Action's position contains scientific and legal errors.

In the third Action, the Office attempted to support this exact same position with the citation of Holash, a post-filing date reference. As detailed in Applicants' third response, neither Holash, nor any other evidence, establishes Fishman as a proper anticipatory reference. Fishman concerns only an inhibitory effect on metastasis. As documented in Holash, at about the time of the present invention, it was "widely accepted that most tumors and metastases originate as small avascular structures" (Holash at introduction) and that, when implanted subcutaneously, "tumor cells do initially grow as space-filling avascular masses" (Holash at discussion). Of particular relevance to melanoma, Holash teaches that tumors "deriving in the skin...may have to go undergo significant growth before they recruit vascular support" (Holash at discussion, emphasis added). Moreover, before the present invention was made, it was known that melanoma cells form avascular tumors (*e.g.*, Alino & Hilario, *Exp. Cell Biol.*, 57(5):246-56, 1989; Exhibit P to Applicants' third response) and that other lung metastases can be avascular (Borgstrom *et al.*, *Anticancer Res.*, 15(3):719-28, 1995; Exhibit Q to Applicants' third response).

Thus, one of ordinary skill in the art would not believe Fishman's initially inoculated B-16 melanoma cells or the lung metastatic foci to be a vascularized tumor, as alleged in the fifth

Action. Indeed, the fifth Action has not offered any proper evidence in support of such a position. Whether or not vascularized tumors can include melanomas, as stated in the present specification, entirely fails to establish Fishman as disclosing a vascularized tumor, which is the relevant enquiry. Thus, Fishman lacks both the *treating* and *vascularized* tumor elements of the claimed invention.

Fishman further fails to teach targeting an aminophospholipid *on the luminal surface of blood vessels of the vascularized tumor*, as required by the claims. The citation of *Bristol-Myers* does not cure the deficiencies of the rejection as there are important differences between the present analyses and the holding in *Bristol-Myers*. For example, in *Bristol-Myers*, the key claim language was found to be non-limiting because (i) it was in the preamble and (ii) it was a voluntary amendment after allowance, neither of which applies to the present claim language, "luminal surface of blood vessels of the vascularized tumor ".

Importantly, Fishman fails to teach any treatment of any tumor by administering an antibody that targets and binds to an *aminophospholipid-protein complex*, such as a *phosphatidylserine-protein complex* (claim 59), and particularly fails to teach administering an antibody that targets and binds to a *phosphatidylserine and β_2-glycoprotein I complex* (claim 60). In fact, the fifth Action does not even acknowledge that the rejected claims include the referenced language. The presently claimed invention is thus even further distinguished from Fishman on these bases.

The anticipation rejection is therefore overcome for the reasons set forth above. Nonetheless, and without acquiescing with the present rejection in any way, Applicants have elected to even further distance the claimed invention from Fishman as suggested in the fifth Action at page 10. In particular, by revising claim 73 to emphasize the therapeutically effective

treatment taught in the present specification, which treatment stems only from the present invention and is not taught in the cited art.

IX. First Rejection Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, 25, 41, 49-55, 57, 58, 61-68, 72, 75-82, 84, 87 and 88 are newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett. Although Applicants respectfully traverse, the Action's concerns are overcome.

In its recent decision addressing the issue of obviousness under 35 U.S.C. §103(a), *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007), the Supreme Court stated that the following factors set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) still control an obviousness inquiry: (1) the scope and content of the prior art; (2) the differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734, 82 USPQ2d at 1388 quoting *Graham*, 383 U.S. at 17-18, 14 USPQ at 467.

The *KSR* Court rejected a rigid application of the "teaching, suggestion, or motivation" test previously applied by the Court of Appeals for the Federal Circuit. *KSR*, 127 S. Ct. at 1739 USPQ2d at 1395. However, the *KSR* Court citing *Graham*, upheld the principle of *avoiding hindsight bias* and cautioned courts to *guard against reading into the prior art the teachings of the invention in issue*. 127 S.Ct. at 1742, 82 USPQ at 1397:

> A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham*, 383 U.S., at 36, 86 S.Ct. 684 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting *Monroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412 (C.A.6 1964)).

Importantly, the Supreme Court in *KSR* stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1389. Following *KSR*, the Board of Patent Appeals and Interferences has stated, "[i]t is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Ex Part El-Naggar*, 2007 WL 2814131 at *3 (citing *In re Hedges*, 783 F.2d 1038, 1041 (Fed. Cir. 1986) (quoting *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965))). Moreover, the Board has also stated that "rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Altenbuchner*, 2007 WL 1766992 at *6 (quoting *In re Kahn*, 441 F3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006)).

Claim 4 is directed to a combination therapy, which requires "*treating* an animal with a *vascularized* tumor by administering a *therapeutically effective combination* of a defined second therapeutic agent and an antibody, or antigen-binding fragment thereof, which *targets* and binds to an aminophospholipid of an *aminophospholipid-protein complex on the luminal surface of blood vessels of the vascularized tumor*". The therapeutically effective amount of the antibody is "an amount effective to kill at least a portion of the endothelial cells of the blood vessels of the vascularized tumor, promote coagulation in at least a portion of the blood vessels of the vascularized tumor, destroy or occlude at least a portion of the blood vessels of the vascularized tumor, induce necrosis in at least a portion of the tumor, induce tumor regression or induce tumor remission". These effects are separately recited in independent claim 71 (kills endothelial cells),

claim 72 (tumor-destructive amount), claim 75 (promotes coagulation), claim 76 (induces tumor regression), claim 77 (induces tumor remission), claim 78 (tumor necrosis-inducing amount) and claim 79 (destroys or occludes).

Dependent claim 6 and independent claim 68 recite that the antibody binds to phosphatidylserine of a phosphatidylserine-protein complex on the luminal surface of blood vessels of the vascularized tumor. Dependent claim 84 specifies that the bound complex is a phosphatidylserine and β_2-glycoprotein I complex on the luminal surface of blood vessels of the vascularized tumor.

The fifth Action at page 4 treats Fishman in the same manner as set forth in the anticipation rejection, and therefore commits the same errors as set forth and corrected above (**Section VIII**). Briefly, Fishman does not teach or suggest *treating* melanoma, but only "an inhibitory effect on metastasis". Inhibition of metastasis is not equivalent to, and does not teach or suggest, methods for treating tumors, as in the presently claimed invention (*e.g.*, Harris declaration throughout, such as paragraphs 16 and 17).

Fishman fails to teach or suggest treating any *vascularized* tumor. In contrast, one of ordinary skill in the art would not believe Fishman's initially inoculated B-16 melanoma cells or the lung metastatic foci to be a vascularized tumor, as alleged in the fifth Action (*e.g.*, Holash, at introduction, discussion; Exhibit P and Exhibit Q to Applicants' third response). The fifth Action has not offered any proper evidence in support of such a position. Importantly, any such evidence would have to show the existence of a vascularized tumor in Fishman, not in Applicants' own specification. *KSR*, 127 S.Ct. at 1742, 82 USPQ at 1397:

Fishman further fails to teach or suggest the important claimed feature of targeting an aminophospholipid *on the luminal surface of blood vessels of the vascularized tumor*, as required

in the present invention. As set forth above, the citation of *Bristol-Myers* does not cure the deficiencies of the rejection. In addition, by treating Fishman exactly the same under § 103(a) as under § 102(b), the fifth Action compounds the legal and scientific errors (see below).

Fishman also fails to teach or suggest any treatment of any tumor by administering an antibody that targets and binds to an *aminophospholipid-protein complex*, such as a *phosphatidylserine-protein complex* (claims 6 and 68), and particularly fails to teach administering an antibody that targets and binds to a *phosphatidylserine and β_2-glycoprotein I complex* (claim 84). In fact, the fifth Action does not even acknowledge that the rejected claims include the referenced language. The presently claimed invention is thus even further distinguished from Fishman on these bases.

Further to the above errors, which apply equally to the § 102(b) and § 103(a) rejections, the fifth Action does not appear to recognize that Fishman is markedly lacking in the suggestion required to be a valid *prima facie* reference under § 103(a). Moreover, Fishman actually teaches away from the claimed invention, which has been completely overlooked by the fifth Action.

Fishman has no teaching or suggestion towards the important claim limitation that the antibody target an aminophospholipid *on the luminal surface of blood vessels of the vascularized tumor*, as required in the present invention. On this point, the fifth Action at page 4 merely states, "while Fishman et al. does not characterize the melanoma as being vascularized, the claimed limitation does not appear to result in a manipulative difference when compared to the prior art", and then cites only Applicants' own specification and *Bristol-Myers*. Applicants' own specification could never be used as a means to render the claimed invention obvious, which has been confirmed by the Supreme Court in *KSR*.

Bristol-Myers also fails to support the rejection in scientific and legal terms. Scientifically, the presently claimed methods are combination therapies, which therefore absolutely have a "manipulative difference" from Fishman. Legally, *Bristol-Myers* concerns only inherent anticipation and expressly excludes a ruling regarding obviousness. Indeed, the entire § 103(a) rejection is based upon an inherency analysis, and reliance on an inherency argument as part of a § 103(a) rejection is improper:

> "The inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown".
>
> *In re Spormann and Heinke*, 150 USPQ 449, 452 (C.C.P.A. 1966).

Moreover, a successful inherency argument can only be established by showing that such "inherency would have been obvious to those skilled in the art when the invention was made". *Kloster Speedsteel AB vs. Crucible Inc.,* 230 USPQ2d 81 (Fed. Cir., 1986). There is no such evidence of record in the present case. In contrast, there is un-rebutted evidence of record showing that the Fishman methods would not inherently treat a *vascularized* tumor, as the inoculated B-16 melanoma cells and resultant lung metastatic foci would not be vascularized (*e.g.*, Holash; Exhibit P and Exhibit Q to Applicants' third response).

The fifth Action also improperly uses the teaching of the present specification in an attempt to support the inherency theories and the obviousness rejection overall, stating "the specification teaches that typical vascularized tumors are solid tumors such as melanomas which require a vascular component for the provision of oxygen and nutrients" (fifth Action at page 4). Whilst the specification may teach that about typical vascularized tumors and solid tumors, the inoculated B-16 melanoma cells and lung metastatic foci in Fishman are not "typical vascularized tumors" or "solid tumors", but rather "space-filling avascular masses" needing "significant

growth before they recruit vascular support" (Holash at discussion). Therefore, by this improper hindsight bias, the fifth Action runs contrary to the Supreme Court's decision in *KSR*.

Another very important difference between Fishman and the presently claimed invention is that Fishman is limited to strategies aimed at binding malignant and cancer cells, including "malignant melanoma cells" (Fishman throughout, *e.g.*, abstract, introduction, Table 1, Figure 1, Figure 3). The presently claimed methods are directed to targeting the blood vessels of vascularized tumors, which are normal cells. These differences were highlighted in Applicants' first and third responses, but have not been acknowledged by the fifth Action.

In addition to lacking a proper suggestion towards the claimed invention, this aspect of Fishman shows that the cited reference actually teaches away from the invention in important respects. In particular, Fishman teaches away from the claimed invention by consistently teaching that phosphatidylserine is not expressed at the surface of normal cells, whereas these are precisely the cells bound by the antibodies in the claimed methods.

For example, Fishman states "cancer cells differ from normal cells by the expression of phosphatidylserine (PS) on their outer membrane surface" (Fishman at abstract). In regard to normal cells, Fishman teaches "phosphatidylserine (PS) is localized exclusively in the inner leaflet of the cell membrane of normal cells" (Fishman in the legend to Figure 3; see also, abstract; page 903, column 1). Fishman continues, "the translocation of PS from the inner to the outer cell membrane is typical of tumor cells" (Fishman in the legend to Figure 3; text at page 903, column 1).

Thus, as the tumor vascular endothelial cells targeted by the presently claimed invention are normal cells, and as Fishman expressly and repeatedly teaches that phosphatidylserine is not expressed at the cell membrane of normal cells, but rather is "localized exclusively in the inner

leaflet", Fishman clearly teaches away from the claimed invention. This overt teaching away in the art has been improperly ignored by the fifth Action: "it is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." *Ex Part El-Naggar*. There is nothing of record to counteract this overt teaching away in the primary reference. The rejection is thus *prima facie* improper and should be withdrawn for this reason.

Moreover, as pointed out in Applicants' first and third responses, by concerning tumor cells, rather than tumor vasculature, Fishman is representative of the standard, but problematic prior art of tumor cell targeting, which is discussed in the background section of the present specification. For example, the specification teaches that both chemotherapeutics and immunotoxins against tumor cells are limited by tumor cell resistance, leading to antigen-negative or antigen-deficient tumor cells, which can survive and repopulate the tumor or lead to further metastases (specification at background). The poor accessibility of tumor cells is another limitation in therapies aimed at tumor cells. The specification teaches that the tumor mass is generally impermeable to molecules of the size of antibodies and immunotoxins, such that the physical diffusion distances and the interstitial pressure within the tumor are significant limitations to therapies aimed at tumor cells (specification at background).

Moreover, this exact line of reasoning was advanced by the third Action to show difficulties in tumor cell treatment. Notably, the third Action at pages 10-12 cited Jain, Dillman and Weiner to show that there are many, many drawbacks in attempting to deliver drugs to tumor cells. These impediments include non-uniform blood delivery to all areas of the tumor; hindered drug delivery and distribution due to increased blood viscosity, high interstitial pressure and

inadequate convection; and problems of tumor cell heterogeneity, shed or internalized targets (third Action at pages 10-12). Although none of these drawbacks apply to the presently claimed methods using antibodies that bind to targets on normal cells at the luminal surface of tumor blood vessels, they are representative of the many problems known in the art of tumor treatment prior to the present invention, and discussed in the specification.

The present inventors developed vascular targeting methods for tumor treatment, at least in part, to overcome the many drawbacks associated with drug delivery to cancer cells, including those enumerated by the third Action. "Recognition of need, and difficulties encountered by those skilled in the field, are classical indicia of unobviousness." *In re Dow Chemical Co.*, 5 USPQ2d 1529 (Fed. Cir. 1988).

Fishman does not teach or suggest any aspect of tumor vasculature targeting, let alone targeting an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, as required by the presently claimed invention. Rather, Fishman generally represents the problematic prior art of tumor cell targeting and, in the context of phosphatidylserine, Fishman *teaches away* from the claimed invention by teaching that phosphatidylserine is not expressed by normal cells. Such teaching away in Fishman is not counteracted by any evidence of record, and the rejection is thus improper and should be withdrawn.

Moreover, targeting an *aminophospholipid-protein complex* on tumor blood vessels is even further removed from any suggestion in Fishman that PS may be exposed on malignant cancer cells. Aminophospholipid-protein complexes may be targeted by the presently claimed invention because the aminophospholipids newly-exposed on the tumor vascular endothelial cells combine, in this membranous environment, with serum proteins, thereby forming aminophospholipid-protein complexes (*e.g.*, specification at page 7). As only the luminal

surfaces of the tumor vascular endothelial cells are exposed to the blood, and not the surfaces of the malignant tumor cells, only the aminophospholipids exposed on tumor vascular endothelial cells can combine with serum proteins to form a *targetable complex*. Accordingly, such claims are even further distinguished over Fishman.

The presently claimed invention is a combination *treatment* method for *vascularized* tumors using an antibody that binds to an aminophospholipid *on the luminal surface of blood vessels of a vascularized tumor*. Fishman does not concern treatment or targeting aminophospholipids on tumor blood vessels, as required in the present claims, let alone by binding to an *aminophospholipid-protein complex*.

Nonetheless, despite the many deficiencies of Fishman, and the overt teaching away in Fishman, the fifth Action cites Fishman against the present claims in combination with Einzig or O'Reilly or Plunkett. The fifth Action agrees that Fishman does not teach the claimed combination treatment (third Action at page 4). Einzig, O'Reilly and Plunkett, whilst generally concerning TAXOL™, endostatin and interleukin-4, respectively, do not teach targeting aminophospholipids on tumor blood vessels or any combination treatment thereof.

Indeed, the fifth Action does not attempt to cite Einzig, O'Reilly or Plunkett for a teaching of aminophospholipid targeting, or even to establish a proper combination with Fishman, but relies simply on the position that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references (fifth Action at page 5). This is in direct contrast to the Supreme Court's decision in *KSR*, which stated that "a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 127 S.Ct. at 1741, 82 USPQ2d at 1389. Moreover, "rejections on obviousness grounds cannot be sustained by mere

conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *Altenbuchner.* Therefore, the rejection as a whole is unfounded and overcome.

In addition, evidence of the surprising effectiveness of a combination therapy of the invention is already of record, demonstrating that tumor treatment using an antibody that binds to an aminophospholipid on the luminal surface of tumor blood vessels and the chemotherapeutic drug, docetaxel, produce synergistic effects (see Exhibit B to Applicants' first response). Phase II Clinical Trials are now underway using a chimeric version of the antibody (Bavituximab) and docetaxel in patients with metastatic breast cancer, and using Bavituximab with other chemotherapeutics, including carboplatin and paclitaxel, in patients with non-small cell lung cancer (NSCLC).

The § 103(a) rejection is thus *prima facie* improper on various grounds, including the many deficiencies of Fishman, none of which are cured by Einzig, O'Reilly or Plunkett. In particular, none of Fishman, Einzig, O'Reilly or Plunkett teaches or suggests combination treatment for vascularized tumors using an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of a vascularized tumor, let alone one that binds to an aminophospholipid-protein complex. Rather, the cited art actually teaches away from the claimed invention.

Nonetheless, and without acquiescing with the present rejection in any way, the claims are even further distinguished from Fishman in view of Einzig, O'Reilly or Plunkett using the language suggested in the fifth Action at page 10. Claims 72, 78 and 79 already correlated with this guidance in the fifth Action, by use of the terms "tumor-destructive amount", "tumor necrosis-inducing amount" and "amount effective to destroy or occlude at least a portion of the

tumor blood vessels", respectively. All but one of the independent claims has been revised to emphasize the therapeutically effective treatment taught in the present specification, which is not suggested in the cited art[1], as acknowledged by the fifth Action at page 10.

The first new § 103(a) rejection is thus overcome and should be withdrawn.

X. Second Rejection Under 35 U.S.C. § 103(a)

Claims 83 and 85 are also newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett in further view of Campbell. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection over Fishman in view of Einzig or O'Reilly or Plunkett is overcome as detailed above (**Section IX**). Campbell is cited for teaching an advantage of monoclonal antibodies over so-called "conventional antiserum" (fifth Action at page 6).

As set forth above, Fishman has many deficiencies, which are not cured by Einzig or O'Reilly or Plunkett, and which the new citation of Campbell also fails to rectify. In particular, none of Fishman, Einzig, O'Reilly or Plunkett, even if combined with Campbell, teach or suggest a *treatment* or a combination *treatment* for *vascularized* tumors using a monoclonal antibody that binds to an aminophospholipid *on the luminal surface of blood vessels of a vascularized tumor*, let alone using a monoclonal antibody that binds to an *aminophospholipid-protein complex* on the luminal surface of blood vessels of a vascularized tumor. In contrast, the art teaches away from the claimed invention.

In any event, and without acquiescing with the present rejection in any way, claims 83 and 85 are even further removed from Fishman in view of Einzig, O'Reilly or Plunkett, combined

[1]Claim 89 is also in condition for allowance as the meaning of "therapeutically effective" set forth in the specification still distinguishes over Fishman.

with Campbell, by using the therapeutically effective treatment language suggested in the fifth Action at page 10.

The second new § 103(a) rejection is thus overcome and should be withdrawn.

XI. Third Rejection Under 35 U.S.C. § 103(a)

Claims 9, 71 and 85 are further newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett in further view of Devaux. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection over Fishman in view of Einzig or O'Reilly or Plunkett is overcome as detailed above (**Section IX**). Devaux is cited for teaching the generation of humanized antibodies, said to reduce immunogenicity and HAMA responses (fifth Action at page 7).

As set forth in Applicants' third response, Devaux is not available as prior art against the present invention, rendering this third § 103(a) rejection entirely improper. In particular, Devaux is a U.S. patent that issued on November 30, 2004, based on an application filed October 27, 2000, which claims priority to two provisional applications, the earliest of which was filed October 29, 1999. Without even considering whether Devaux's claims for priority are proper, Devaux is not prior art against the present invention as the earliest possible date of Devaux (October 29, 1999) is after each of the July 13, 1998 and July 12, 1999 priority dates for the present application.

In any event, Fishman has many deficiencies, which are not cured by Einzig or O'Reilly or Plunkett. Even if Devaux was available as prior art, Devaux fails to address the deficiencies of Fishman, Einzig, O'Reilly and Plunkett. In particular, none of Fishman, Einzig, O'Reilly or Plunkett, even if combined with Devaux, teach or suggest a *treatment* or a combination *treatment* for *vascularized* tumors using a humanized antibody that binds to an aminophospholipid *on the*

luminal surface of blood vessels of a vascularized tumor, let alone using a humanized antibody that binds to an *aminophospholipid-protein complex* on the luminal surface of blood vessels of a vascularized tumor. In contrast, the art teaches away from the claimed invention.

Irrespective, and without acquiescing with this rejection in any way, claims 9, 71 and 85 are even further removed from Fishman in view of Einzig, O'Reilly or Plunkett, even if combined with Devaux, by using the therapeutically effective treatment language suggested in the fifth Action at page 10.

The third new § 103(a) rejection is thus overcome and should be withdrawn.

XII. Fourth Rejection Under 35 U.S.C. § 103(a)

Claims 8 and 70 are also newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett in further view of Nicolotti. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection over Fishman in view of Einzig or O'Reilly or Plunkett is overcome as detailed above (**Section IX**). Nicolotti is cited for teaching that antibody fragments, rather than whole antibodies, are better suited for *in vivo* use (fifth Action at page 8). However, as taught in the present specification, and in contrast to Nicolotti, antibody fragments may not always be better suited for *in vivo* use than whole antibodies in the context of the present invention. For example, the specification teaches that anti-aminophospholipid antibodies for use in inducing complement-mediated lysis will generally include the Fc portion of the antibody (specification at page 14).

Aside from the foregoing issues, Fishman has many deficiencies, which are not cured by Einzig or O'Reilly or Plunkett, and which the new citation of Nicolotti also fails to rectify. In particular, none of Fishman, Einzig, O'Reilly or Plunkett, even if combined with Nicolotti, teach

or suggest a combination *treatment* for *vascularized* tumors using an antigen-binding fragment of an antibody that binds to an aminophospholipid *on the luminal surface of blood vessels of a vascularized tumor*, let alone one that binds to an *aminophospholipid-protein complex* on the luminal surface of blood vessels of a vascularized tumor. In contrast, the art teaches away from the claimed invention.

In any event, and without acquiescing with the present rejection in any way, claim 8 is even further removed from Fishman in view of Einzig, O'Reilly or Plunkett, combined with Nicolotti, by using the therapeutically effective treatment language suggested in the fifth Action at page 10.

The fourth new § 103(a) rejection is thus overcome and should be withdrawn.

XIII. Fifth Rejection Under 35 U.S.C. § 103(a)

Claim 23 is next newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett in further view of Wolff. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection over Fishman in view of Einzig or O'Reilly or Plunkett is overcome as detailed above (**Section IX**). Wolff is cited for teaching that antibody dimers have advantages as compared to antibody monomers (fifth Action at page 8).

As set forth above, Fishman has many deficiencies, which are not cured by Einzig or O'Reilly or Plunkett, and which the new citation of Wolff also fails to rectify. In particular, none of Fishman, Einzig, O'Reilly or Plunkett, even if combined with Wolff, teach or suggest a combination *treatment* for *vascularized* tumors using an antibody dimer that binds to an aminophospholipid *on the luminal surface of blood vessels of a vascularized tumor*, let alone using an antibody dimer that binds to an *aminophospholipid-protein complex* on the luminal

surface of blood vessels of a vascularized tumor. In contrast, the art teaches away from the claimed invention.

In any event, and without acquiescing with the present rejection in any way, claim 23 is even further removed from Fishman in view of Einzig, O'Reilly or Plunkett, combined with Wolff, by using the therapeutically effective treatment language suggested in the fifth Action at page 10.

The fifth new § 103(a) rejection is thus overcome and should be withdrawn.

XIV. Sixth Rejection Under 35 U.S.C. § 103(a)

Finally, claim 27 is newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over Fishman in view of Einzig or O'Reilly or Plunkett in further view of Moossa. Although Applicants respectfully traverse, the Action's concerns are overcome.

The rejection over Fishman in view of Einzig or O'Reilly or Plunkett is overcome as detailed above (**Section IX**). Moossa is cited for teaching that melanoma treatment includes surgical excision (fifth Action at page 9).

As detailed above, Fishman has many deficiencies, which are not cured by Einzig or O'Reilly or Plunkett, and which the new citation of Moossa also fails to rectify. In particular, none of Fishman, Einzig, O'Reilly or Plunkett, even if combined with Moossa, teach or suggest a combination *treatment* for *vascularized* tumors using an antibody that binds to an aminophospholipid *on the luminal surface of blood vessels of a vascularized tumor*, let alone using an antibody that binds to an *aminophospholipid-protein complex* on the luminal surface of blood vessels of a vascularized tumor. In contrast, the art teaches away from the claimed invention.

In any event, and without acquiescing with the present rejection in any way, claim 27 is even further removed from Fishman in view of Einzig, O'Reilly or Plunkett, combined with Moossa, by using the therapeutically effective treatment language suggested in the fifth Action at page 10.

The sixth new § 103(a) rejection is thus overcome and should be withdrawn.

XV. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, all present claims are in condition for allowance. Should Examiner Fetterolf have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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